# ANCA-associated vasculitis

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# Chapter 7

## Venous thromboembolism in ANCA-associated vasculitis. Incidence and risk factors

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Rheumatology 2008;47:530-534
Nederlands Tijdschrift voor Geneeskunde; in press

## Abstract

### *Objectives*

In patients with ANCA-associated vasculitis (AAV), an increased incidence of venous thromboembolism (VTE), mainly during active disease, has been described. In a large cohort of AAV patients, we assessed the incidence of VTE and its relation with disease activity and classic risk factors for VTE.

### *Methods*

Patients newly diagnosed with AAV between 1990 and 2005 and treated with cyclophosphamide and corticosteroids were included. Data were retrospectively retrieved from charts and using a questionnaire. The incidence of VTE associated with and following a diagnosis of AAV was calculated (VTE/100 person-years) and related to periods with active disease.

### *Results*

One hundred and ninety-eight patients with AAV were followed for 6.1 (0.2-17.6) years. In 23 patients (12%), 25 VTEs (17 deep venous thromboses, 3 pulmonary emboli, 5 both) occurred in association with AAV, of which 52% occurred during active disease, defined as 3 months before and after diagnosis or relapse of AAV. Overall, VTE incidence was 1.8/100 person-years, increasing to 6.7/100 during active disease. VTEs occurred significantly less frequently in patients with WG than in patients with microscopic polyangiitis and renal limited vasculitis. Classic risk factors were present in most patients at some moment during follow-up. There were no significant differences in classic risk factors between patients with and without AAV-associated VTE.

### *Conclusions*

Patients with AAV have an increased risk of developing VTEs, especially when AAV is active. This finding could not be explained by classic risk factors, but is probably related to endothelial changes and hypercoagulability induced by AAV and its therapy.

## Introduction

ANCA-associated vasculitis (AAV) constitutes a group of primary vasculitides associated with ANCA. AAV comprise WG, microscopic polyangiitis (MPA), renal limited vasculitis (RLV) and the Churg-Strauss syndrome (CSS). AAV is localized in small- and medium-sized vessels, and frequently affects the kidneys and the upper and lower airways.

It is remarkable that even with a short period of inflammation, like urinary tract or airway infection, the risk of venous thromboembolism (VTE) appears increased (1). In autoimmune diseases with chronic inflammation, like SLE (2) and inflammatory bowel disease (3), an elevated risk of VTE has been found as well. Though deep venous thrombosis (DVT) and pulmonary embolism (PE) have been described in AAV patients (4, 5), the incidence of VTE in these patients has not been studied until recently. In a prospective study, Merkel et al. (6) found an increased incidence of 7.0/100 person-years of VTE in WG patients. For comparison, in healthy Swedish men the incidence is 0.3/100 person-years (7). The cause of this increased incidence of VTE in WG patients cannot be derived from the study of Merkel et al. (6), as the prevalence of classic risk factors for VTE, like immobilization and major surgery (8), was not investigated. However, they noticed that most VTEs developed during periods of active disease. A comparable incidence of VTE (4.3/100 person-years) was seen in another, retrospective study, in which VTEs occurred mainly during active disease (9).

Using a retrospective design, we investigated the incidence of VTE in our cohort of patients with AAV. Furthermore, we evaluated the influence of disease activity and the presence of classic risk factors for VTE on the occurrence of VTE.

## Methods

Our cohort included all patients who were diagnosed with AAV between January 1990 and February 2005, according to the Chapel Hill Consensus Conference definitions (10), and who were treated with cyclophosphamide and corticosteroids for induction of remission. This criterion was chosen to create a homogeneously treated cohort and to exclude the possible influence of different treatment modalities on the development of VTE. Patients diagnosed with CSS were excluded as these patients are usually not primarily treated with cyclophosphamide.

The data used for the study were retrieved from the patients medical records. To complete our data, we interviewed all patients, if possible, using a questionnaire. We recorded all VTEs that had occurred, either before or after the diagnosis of AAV was made and assessed how the diagnosis of VTE was established. VTEs occurring in association with a central venous catheter were excluded. Besides these characteristics, we analysed the prevalence of classic risk factors of VTE: immobilisation (at least 3 days), trauma, major surgery, malignancy, pregnancy, the use of oral anticonceptives and hormonal replacement therapy, heart failure, haematological disease, diabetes mellitus, smoking, atrial fibrillation, positive family history, obesity and thrombophilia (8). These risk factors had to be prevalent during a period of 4 weeks

preceding a VTE or, if the patient did not develop a VTE, during total follow-up, starting 3 months before diagnosis of AAV.

### *Calculations*

The incidence of VTE associated with AAV was calculated as the number of VTEs occurring during 100 person-years of follow-up. For this calculation, we counted all VTEs in patients after diagnosis of AAV, adding a period of 3 months before the diagnosis of AAV was made. We added this period because, due to a diagnostic delay, in most cases AAV had been active some time before the diagnosis was made. VTEs occurring in this period were considered AAV associated. VTEs occurring more than 3 months before diagnosis of AAV were not considered to be AAV associated. To assess whether disease activity influenced the development of VTE, we calculated the incidence in periods with both active and inactive disease; active disease was defined as a period of 3 months before and 3 months after diagnosis or relapse. A relapse was defined as new or increasing disease activity requiring use of renewed or intensified immunosuppressive therapy. To measure disease activity, we used the Birmingham Vasculitis Activity Score (BVAS) (11). In addition, we compared demographic and disease characteristics and risk factors in patients who developed a VTE associated with AAV and those who did not develop a VTE during the period starting 3 months before the diagnosis of AAV.

Differences in proportions between groups were tested using the Fisher's exact test or chi-square test, when appropriate. Numerical data between groups were compared using the Mann-Whitney U-test and the chi-square test. A two-sided p-value $<0.05$ was considered to indicate statistical significance.

## Results

### *Patients*

A total of 198 patients met our inclusion criteria. Table 1 shows the demographic and disease characteristics of the cohort. Of these 198 patients, 33 died and 23 were lost to follow-up. From these patients, only data retrieved from their medical records could be used. In all other patients, a questionnaire was completed at the first visit at our outpatient clinic between February and July 2006.

In our cohort, the majority (72%) was diagnosed with WG and 98% of all patients were ANCA-positive at diagnosis. The median observation period since diagnosis of AAV was 6.1 years (range: 0.2–17.6).

Table 1: Demographic and disease characteristics of the patients at diagnosis

| Characteristics | AAV-associated VTE* n = 23 | No AAV-associated VTE* n = 175 |
|---|---|---|
| Number of VTEs | 25 | 3* |
| Age, median (range), years | 60 (22-86) | 55 (14-81)# |
| Gender | | |
| Male | 13 (57) | 105 (60) |
| Female | 10 (43) | 70 (40) |
| Diagnosis | | |
| WG | 10 (43) | 133 (76)## |
| MPA | 7 (30) | 27 (15) |
| RLV | 6 (26) | 15 (9) |
| Organ involvement | | |
| Renal | 16 (70) | 111 (63) |
| Lung | 10 (43) | 81 (46) |
| Renal and lung | 8 (35) | 60 (34) |
| ANCA-specificity | | |
| PR3 | 11 (48) | 135 (77)^ |
| MPO | 11 (48) | 34 (19) |
| Other | 1 (4) | 3 (2) |
| Negative | 0 | 3 (2) |
| BVAS, median (range) | 23 (12-38) | 21 (5-48) |
| Positive history of VTE | 2 (9) | 18 (10) |
| Exposition to active disease , median (range), months** | 12 (6-72) | 12 (6-36) |
| Observation period, median (range), years | 6.8 (0.2-15.7) | 6.0 (0.2-17.6) |

WG = Wegener Granulomatosis; MPA = Microscopic Polyangiitis; RLV = Renal Limited Vasculitis; VTE = venous thromboembolism; BVAS = Birmingham Vasculitis Activity Score at diagnosis of AAV. Percentages between brackets unless otherwise indicated.

* VTEs were considered AAV-associated when occurring 3 months before, or after diagnosis of AAV.

In the group with no AAV-associated VTE, 3 VTEs occurred in 3 patients more than 3 months before diagnosis of AAV. In 2 patients who later developed an AAV-associated VTE, 5 VTEs occurred not in association with AAV.

** Active disease was defined as 3 months before and after diagnosis or relapse of AAV.

# p = 0.11, ## p = 0.0023; diagnosis of WG compared to other diagnoses, ^ p = 0.0049; comparing PR3-ANCA to other ANCA specificities.

### *VTEs*

Table 2 shows the VTEs that occurred in our cohort. In total, 25 VTEs occurred in 23 patients (12%): 17 DVTs, 3 PEs and 5 episodes of both a DVT and PE at the same time. Of these 25 VTEs, 23 occurred at or after the diagnosis of AAV was made, while 2 VTEs occurred in the period of 3 months prior to diagnosis of AAV. The median time to develop a VTE after diagnosis of AAV was 8.8 months (range: 0-139). The incidence of VTEs occurring in the period starting 3 months before and following the diagnosis of AAV was 1.8/100 person-years. In five patients, another eight VTEs occurred more than 3 months (median 91, range: 20-612) before the diagnosis of AAV (Figure 1). These eight VTEs were not considered as AAV associated. In two of these five patients, VTE recurred in association with AAV.

Thirteen of 25 VTEs (52%) occurred within a period of 3 months prior to or following a diagnosis of active AAV (Figure 1). Table 3 shows the VTEs during episodes of presence and absence of active AAV. The incidence of VTE during active disease was 6.7/100 person-years compared with 1.0/100 person-years in periods without active disease ($p<0.0001$). Using a period of 6 months prior to or following active AAV to define active disease, this incidence would have been 4.1/100 person-years in periods with active and 0.9/100 person-years in periods without active disease.

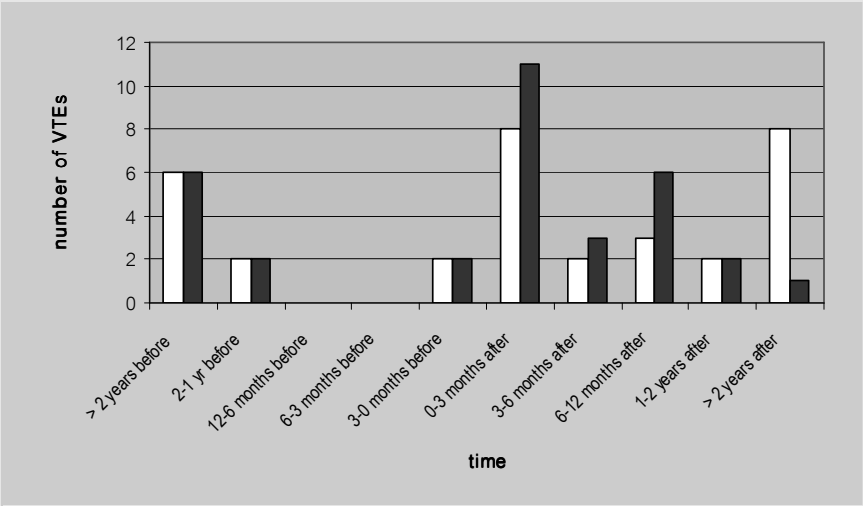
**Table 2: Venous Thromboembolisms in AAV patients**

| **23 patients (12% of studied cohort)** | |
|---|---|
| Number of VTEs | |
| Associated with AAV* | 25 |
| First VTE | 21 |
| Recurrence | 4 |
| Type of VTE (%) | |
| DVT leg | 17 (68) |
| PE | 3 (12) |
| DVT and PE | 5 (20) |
| Diagnosis | |
| DVT | |
| Ultrasound | 14 |
| Ultrasound and phlebography | 1 |
| Unknown | 2 |
| PE | |
| Ventilation/perfusion scintigraphy | 3 |
| DVT and PE | |
| Ultrasound and ventilation/perfusion scintigraphy | 3 |
| Ultrasound and CT-thorax | 2 |
| CRP**, median (range), mg/dl (normal <10) | 16 (2-190) |

* VTEs were considered AAV-associated when occurring 3 months before, or after diagnosis of AAV. ** CRP at time of VTE. VTE = venous thromboembolism; AAV = ANCA associated vasculitis; DVT = deep venous thrombosis; PE = pulmonary embolism. ercentages between brackets unless otherwise indicated.

Table 1 compares the features of the patients who developed a VTE associated with AAV and the patients who did not develop a VTE shortly before or following a diagnosis of AAV. The median age in the VTE group was slightly, but not significantly ($p=0.11$), higher than that in the group that did not develop a VTE. A diagnosis of WG ($p=0.0023$) and ANCA-specificity for proteinase 3 (PR3) ($p=0.0049$) were significantly less frequent in the VTE group than in the group that did not develop a VTE within the defined period. Having a history of VTE occurring for more than 3

**Figure 1. Number of VTEs in relation to diagnosis and disease activity**




Horizontal axis: time either in relation to moment of diagnosis (white bars) or to moment of AAV being active (diagnosis or relapse) (black bars). White bars: 33 VTEs that occurred in our cohort, in relation to the moment of diagnosis. Twenty-five VTEs were considered AAV associated as they occurred 3 months before or after diagnosis of AAV. Black bars: 33 VTEs that occurred in our cohort, in relation to disease being active. The period in which AAV was considered active was defined as 3 months before and after diagnosis or relapse of AAV. Thirteen VTEs occurred during active disease.

months before diagnosis of AAV was infrequent (2.5%) and not different between both groups. No differences were found in the duration of exposition to active disease and the disease activity at diagnosis between the two groups. Seven of the 33 patients who died had experienced a VTE. Six of these VTEs were AAV associated (three VTEs occurred during active disease), while one occurred more than 5 years before diagnosis. In none of these patients VTE was the likely cause of death.

**Table 3: Incidence of AAV-associated VTE during active and inactive disease**

| | All VTE | VTE during active disease | VTE during inactive disease |
|---|---|---|---|
| Events | 25 | 13 | 12 |
| Total observationperiod, years | 1379 | 194 | 1185 |
| Incidence/100 person-years | 1.8 | 6.7 | 1.0* |

Active disease was defined as 3 months before and 3 months after diagnosis or relapse of AAV. * p <0.0001

### *Classic risk factors of VTE in AAV patients*

Table 4 shows the distribution of classic risk factors for VTE in patients who developed a VTE and those who did not develop an AAV-associated VTE. A median of 1 (range: 0-3) risk factor for VTE was present during a period of 4 weeks preceding a VTE. In patients who did not develop an AAV-associated VTE, 1 (range: 0-6) risk factor was present at least once during follow-up. There were no significant differences in the presence of risk factors between the groups with and without AAV-associated VTE. Though not significant, immobilization was slightly more present in the patients (n=7, 30%) who developed a VTE during a period of 4 weeks preceding the VTE, compared with the group of patients who did not develop an AAV-associated VTE, in which 26 patients (15%) were immobilized at least once during follow-up (p=0.07). A positive family history for VTE was present in only one patient in the VTE group (4%) and infrequently prevalent in the group that did not develop an AAV-associated VTE (10%) (p=0.70). No differences in the prevalence of obesity were seen between those with and without a VTE (p=0.48). In the group of patients who did not develop an AAV-associated VTE, 18 patients (10%) used coumarins for some time during follow-up, all for indications other than VTE. However, these 18 patients used the coumarins for a median period of 12 months (range: 2-96) only, while they were followed for 4.5 years. In only one of these 18 patients, coumarins were used during a period of active disease.

In only nine (39%) patients, who had developed a VTE, tests for thrombophilia were performed. Four patients had elevated levels of factor VIII (251, 352, 492 and 415%) and three of these had elevated levels of von Willebrand factor (253, 314 and 296%) as well. All patients tested for lupus anti-coagulans (n=4) and for anti-cardiolipin antibodies (n=5) were found negative. There were no patients with mutations or with other abnormalities of (anti-) coagulation factors.

**Table 4: Distribution of classical risk factors for VTE in the two different groups of patients**

| | AAV-associated VTE (n=23) | No AAV-associated VTE (n=175) |
|---|---|---|
| Risk factors (%) | | |
| 0 | 10 (40) | 48 (27) |
| 1 | 10 (40) | 62 (35) |
| 2 | 2 (8) | 40 (23) |
| 3 | 3 (12) | 19 (11) |
| ≥ 4 | 0 | 6 (3) |
| Number of risk factors, median (range) | 1 (0-3) | 1 (0-6) |
| Risk factor (%) | | |
| Immobilisation | 7 (30) | 26 (15) |
| Trauma | 0 | 4 (2) |
| Major surgery | 1 (4) | 16 (9) |
| Malignancy | 1 (4) | 15 (9) |
| Pregnancy | 0 | 9 (5) |
| Oral anticonceptives | 2 (9) | 14 (8) |
| HRT | 0 | 9 (5) |
| Heart failure | 3 (13) | 14 (8) |
| Hematologic disease | 0 | 2 (1) |
| Diabetes Mellitus | 3 (13) | 21 (12) |
| Smoking | 5 (22) | 39 (23) |
| Atrial fibrillation | 1 (4) | 7 (4) |
| Family history | | |
| Positive | 1 (4) | 18 (10) |
| Negative | 12 (52) | 84 (48) |
| Unknown | 10 (43) | 77 (42) |
| Body mass index | | |
| <25 | 3 (13) | 36 (21) |
| 25-30 | 7 (30) | 43 (25) |
| >30 | 2 (9) | 28 (16) |
| Unknown | 11(48) | 68 (39) |
| Coumarins* | 0 | 18 (10) |

HRT = hormonal replacement therapy.

* Coumarins for other indications than VTE treatment.

Risk factors in the group of patients with AAV-associated VTE had to be present in the 4 weeks preceding the VTE. For the no AAV-associated VTE group, the risk factors had to be present in the period 3 months before or after diagnosis of AAV. Percentages between brackets unless otherwise indicated. No significant differences were found between the two groups.

## Discussion

In this study, we investigated the incidence of VTE in a large homogeneous cohort of AAV patients and the possible influence of disease activity and classic risk factors for VTE on the occurrence of VTE. We found an increased incidence of VTE just prior to and after the diagnosis of AAV of 1.8/100 person-years, compared with 0.3 in a healthy population of the same age (7). As 52% of VTEs occurred within a period of 3 months prior to or following a diagnosis of active AAV, the incidence increased to 6.7/100 person-years in periods with active AAV. Even when AAV was inactive, the incidence was still rather high (1.0/100 person-years). VTEs occurred less frequently in patients with WG and in those with PR3-ANCA. As classic risk factors for VTE were present at some point of time in almost all patients, we found no significant differences in prevalence of these risk factors between patients who developed an AAV-associated VTE and those who did not. These results must be seen in the context of the retrospective design of this study. We may have missed (asymptomatic) VTEs, which could have been diagnosed in a prospective study. On the other hand, we checked all the information retrieved from the medical charts by interviewing the patients.

The incidence of VTE of 1.8/100 person-years in our cohort is higher than the incidence of VTE in SLE patients (1.0) (2), but lower than in patients with a positive history of VTE (7.2) (12). Only one prospective study has analysed the incidence of VTE in 180 WG patients (6). Similar to our observations, they found an increased incidence (7.0/100 person-years) of VTEs, mainly (83%) occurring 2 months prior to or following a diagnosis of active disease. If the seven VTEs that occurred in this study within 3 months before diagnosis were also included, like in our study, the incidence would have increased to 8.0/100 person-years. The incidence of VTE found in our study is much lower which can be explained by the longer duration of our observation period (2.6 vs 6.1 years), which decreases the relative exposure to periods with active disease in our study. In line with this hypothesis is our finding that the incidence of VTE increased to 6.7/100 person-years when assessing periods with active disease only. The finding that 10% of our patients who did not develop an AAV-associated VTE used coumarins, could not explain that the incidence of VTEs was lower than that in aforementioned prospective study by Merkel et al. (6). Our patients used coumarins for 12 months only, while follow-up was 4.5 years, and only one patient used coumarins during active disease. The retrospective study of Weidner et al. (9) also showed an increased incidence of VTE of 4.3/100 person-years in 105 patients with AAV. Again, VTEs occurred mainly during active disease (81%), though, as stated in their discussion, a validated tool to assess disease activity was not used in this study, which makes it difficult to compare their results with ours. In contrast to Weidner et al. (9), we found that VTEs were less prevalent in WG patients (43 vs 62%) than in patients with MPA and RLV, and in patients with PR3-ANCA vs those with MPO-ANCA (48 vs 76%). The reason for these discrepancies is not clear.

A median of one classic risk factor for VTE was present in the 4 weeks prior to the diagnosis of VTE in our patients. Immobilization prior to VTE occurred more frequently, in patients with an AAV-associated VTE, though this difference was not significant ($p=0.07$). Furthermore, in the group without an AAV-associated VTE, 18

patients (10%) used coumarins compared with no one in the AAV-associated VTE group, though the use of coumarins was not significantly different between the two groups (p=0.14). Interpretation of differences in the prevalence of risk factors in our study is problematic, since a period of 4 weeks is compared with a period of (median) 6.1 years. Furthermore, the numbers of both VTEs and prevalence of classical risk factors were low in comparison to the number of episodes of active AAV disease, which may have precluded finding any significant differences. In the study by Weidner et al. (9), no classical risk factors were prevalent.

The cause of the increased risk of VTE in AAV patients, especially when the disease is active, is unknown. Even during short periods of inflammation, like urinary tract and airway infections, an elevated risk of VTE seems to be present (1). This association is also seen in chronic inflammatory diseases like inflammatory bowel disease (3). Changes in endothelial function and hypercoagulability, especially during active disease, could explain this risk of VTE. It is tempting to speculate that loss of anti-thrombogenic activity of endothelium resulting from damage and activation during inflammation plays a role. Both cytokines and ischaemia are known to cause endothelial damage (13). Circulating ANCA may also cause endothelial damage, particularly following an interaction between ANCA and neutrophils on the endothelial surface (reviewed in ref. (14)). Furthermore, circulating ANCA can possibly interact with PR3 and MPO expressed by or bound to endothelial cells (14), although this is still controversial. In line with these data, circulating endothelial cells as a marker for endothelial damage have been detected in AAV patients, especially when AAV is active (14). However, these procoagulant changes of endothelium during inflammation have so far only been noted in arterial vessels. How venous endothelium functions in systemic vasculitis is still unknown.

Hypercoagulability, mainly during active disease, can also be present in patients with AAV. Observations supporting a hypercoagulable state in patients with active AAV include the detection of high levels of D-dimers and thrombin–antithrombin III complexes in these patients, reflecting activated clotting (15). The extrinsic coagulation pathway becomes active when endothelium is activated or damaged by increased expression of tissue factor, which also activates factor VIII (16). This process is stimulated by pro-inflammatory cytokines, like TNF-$\alpha$ (17) and IL-1 (16). Elevated levels of factor VIII are often seen in AAV patients (18), which is known to increase the risk of VTE (19). Inflammation and renal disease may induce elevated levels of factor VIII. In our study, four out of the nine patients, tested for factor VIII, indeed had elevated levels of factor VIII. Increased platelet aggregation (13) and decreased fibrinolytic capacity (20) during active disease, have also been described as causes for thrombosis in AAV patients. Furthermore, fibrinogen, an acute-phase protein, might contribute to the occurrence of VTEs by increasing blood viscosity and enhancing platelet aggregation, though in a large prospective study no association between fibrinogen levels and VTEs was noted (21). In addition, loss of anti-thrombogenic factors, such as anti-thrombin III and protein C, due to significant proteinuria can be present as well (4). In our study, renal involvement was present in most patients who developed a VTE, although a full-blown nephrotic syndrome was absent (data not shown).

Antiphospholipid antibodies, known for their association with VTE, are detectable in patients with AAV (4;22). One study reported presence of these antibodies in 19% of WG patients (22). However, these antibodies are often not detected in repeated tests and the majority of these patients did not develop a VTE (5). It seems

likely that these antiphospholipid antibodies are rather an epiphenomenon, associated with hypergammaglobulinaemia or antigen exposition on endothelium (5;22). Unfortunately, our population was insufficiently tested for these antibodies.

The treatment with cyclophosphamide and high doses of corticosteroids may also explain the increased incidence of VTE in AAV patients. Combination chemotherapy containing cyclophosphamide is known to increase the risk of VTE (reviewed by Haddad and Greeno (23)). Chemotherapeutic agents can cause damage to the vascular endothelium, induce apoptosis of endothelial cells and platelet activation and release cytokines. In addition, a decrease in the levels of anti-coagulant proteins C and S can be seen, as well as an increase in plasminogen inhibitor 1 (PAI-1) as was demonstrated in patients who were treated with cyclophosphamide in combination with methotrexate and fluoracil (CMF for treatment of breast cancer). High doses of corticosteroids can also be thrombogenic for they may both induce elevated levels of factor VIII (24) and a hypofibrinolytic state (25).

Whether the increased incidence of VTE in patients with (active) AAV justifies prophylaxis against VTE is presently unclear. Currently, prophylaxis, proven safe and effective, is recommended for acutely ill patients who are bedridden and/or have risk factors for thrombosis, like inflammatory bowel disease and malignancy (26). To also provide prophylaxis to hospitalized AAV patients with active disease, who are at risk as well, seems reasonable. Randomized studies to evaluate both the protective effect of prophylaxis and the risk of bleeding should be performed as the incidence of VTE during periods of active AAV is in the same order of magnitude as for example in patients with a history of VTE in whom prophylaxis is considered.

In conclusion, we found an increased risk of VTE in AAV patients, especially during active disease. Classic risk factors for VTEs were, to some extent present, prior to VTE, but also occurred frequently in patients who did not develop a VTE. The underlying mechanism for this increased risk of VTE is unknown, but is likely to be associated with changes in endothelial function and integrity, and with induction of a state of hypercoagulability resulting from changes in pro- and anti-coagulant factors associated with inflammation and its therapy. It seems justified to conclude that physicians should be alert for the development of VTE in AAV patients, especially during active disease. More research is needed to clarify the cause of the high incidence of VTE in patients with (active) AAV and to establish whether and when prophylaxis against VTE should be started.

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